



REVIEW ARTICLE

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A Path for Horizing Your Innovative Work

PHARMACOKINETIC OF RENAL FAILURE THERAPY

***C.M. MODI, F. D. MODI, S. K. MODY, H. B. PATEL**

Department Of Pharmacology and Toxicology College of Veterinary Science and Animal

Husbandry Sdau Sardarkrushinagar - 385506, Gujarat, India

Corresponding Author Email: chiragvets@yahoo.co.in

Abstract: Renal failure (loss of kidney normal functionality) is characterized by the reduction in the excretory and regulatory functions of the kidney. It usually occurs at the terminal stages of the disease processes. The Kidney is the primary organ responsible for the excretion of drugs and their metabolites. Risk factors for the development of nephrotoxicity for selected high-risk therapies, e.g. aminoglycosides, NSAIDs, amphotericin B, antineoplastics, ACE inhibitors, angiotensin II receptor blockers. Beside these, drug administered along with certain known nephrotoxic compounds as well as administration of drugs in hepatic disorders may also progressively influence kidney functioning. Methods that have been used to evaluate kidney function in veterinary medicine include determination of serum creatinine and BUN concentrations. Impaired renal function alters pharmacokinetics of drugs, which are mainly eliminated via kidney. Changes arising from renal impairment are decrease in renal excretion, or possibly renal metabolism. Other changes include changes in absorption, hepatic metabolism, plasma protein binding and drug distribution. The pathophysiological mechanism responsible for alterations in drug disposition, especially metabolism and renal excretion is the accumulation of uraemic toxins that may modulate cytochrome P450 enzyme activity and decrease glomerular filtration as well as tubular secretion. Dosage regimen adjustment is mainly considered in renal diseases, when the drug is mainly (at least 70% of the dose) excreted by the kidney either unchanged or as an active metabolite or the therapeutic window of the drug or the metabolite is narrow.

Keywords: Renal failure, pharmacokinetics, dosage regimen.

INTRODUCTION

Renal failure is a condition where the kidneys lose their normal functionality. It is characterized by the reduction in the excretory and regulatory functions of the kidney. It usually occurs at the terminal stages of the disease processes. Kidney failure - when one or both kidneys are not able to perform their usual functions. Their main function is to remove waste from the body and to balance the water and electrolyte content of the blood by filtering the salt and water in the blood. The waste and water excreted by the kidneys combine to form urine.

The Kidney provides the final common pathway for the excretion of most drugs and their metabolites and is subjected to high concentrations of potentially toxic substances. As a result, many groups of drugs can cause renal damage, especially in the presence of pre-existing renal disease. The proliferation of new drugs and their diverse actions makes prescribing for patients with renal disease both difficult and hazardous¹.

Any alterations in the normal pathway of the kidneys it leads to renal failure. Renal failure is of two types - acute and chronic.

Acute renal failure when diagnosed early is totally curable. Chronic renal failure is seldom curable, even leading to death in severe cases. Methods that have been used to evaluate kidney function in veterinary medicine include determination of serum creatinine and BUN concentrations².

TYPES OF RENAL FAILURE

ACUTE RENAL FAILURE The kidneys abruptly stop working entirely or almost entirely but may eventually recover nearly normal function. (Hilton, 2006)

CHRONIC RENAL FAILURE An irreversibly and progressive loss of renal functions, resulting in a verity of clinical and laboratory changes due to reduced renal excretory, endocrine and regulatory functions.

CAUSES OF RENAL FAILURE

NON INFECTIOUS CAUSE

- **Aminoglycosides** (Amikacin, Gentamycin, Tobramycin)

In the kidney aminoglycosides bind to renal cortical tissue and cause proximal tubular

necrosis. Concentration in the renal cortex may reach 10 times that in the plasma.³

- **NSAIDs (Ibuprofen, Naproxen)**

NSAIDs are generally safe and effective, but they inhibit prostaglandin, which cause vasodilatation at the afferent arterioles and the maintain renal circulation. It cause interstitial nephritis, reduced sodium excretion, and possibly, damage to the renal tubular epithelium. These effects can develop slowly and without relation to duration of use or dosage, although interstitial nephritis can also occur as an acute, often allergic, response to NSAIDs.^{4,5}

- **Amphotericin B**

It causes renal vasoconstriction, followed by damage to the glomeruli and tubules. Early tubular damage is associated with increased excretion of uric acid and severe tubular loss of potassium

- **Anti neoplastics (Carboplatin, Cisplatin)**

- **ACE inhibitors**

ACE (Angiotensin-converting enzyme) inhibitors, Angiotensin receptor blockers (ARBs), or both are recommended as first line treatment for hypertension in people with diabetes or with nondiabetic

proteinuria. ACE inhibitors act to inhibit production of Angiotensin II; ARBs inhibit the Angiotensin II receptors. Because of their intraglomerular effects, the rate of proteinuria declines, which will slow the progression of chronic kidney disease to stage 5. Thus ACE inhibitors and ARBs are renoprotective. Acute renal failure induced by ACE inhibitors or ARBs usually reverses within two to three days of discontinuing the drug. It occurs more often in hypotensive patients, those with renal artery stenosis, or those with fluid volume depletion or dehydration; in such cases, it's important to replace lost fluids. Drug therapy can often be reinstated once hemodynamic stability is restored.⁶

- **Angiotensin II receptor blockers**

It may cause pressure-induced renal injury via its ability to induce systemic and glomerular hypertension or cause ischemia-induced renal injury secondary to intra renal vasoconstriction and decrease renal blood flow. It may also cause tubular injury secondary to angiotensin-induced proteinuria. Blocking the RAS (renin-angiotensin system) in subjects with renal disease, because angiotensin II has hemodynamic and non hemodynamic

mechanism by which it can cause renal damage.⁷

- **Radiographic contrast media**

It can also produce tubular damage. Radiographic dye usually promotes an osmotic diuresis and urine losses of up to 7 ml for every 1 ml of dye used.

INFECTIOUS CAUSES

- Hypovolemia
- Rhabdomyolysis
- Nephrosis
- Glomerulonephritis
- Prostate Cancer
- Kidney Stones
- Poorly Control Diabetes
- Chronic Glomerulonephritis
- Polycystic Kidney Disease

DRUG INDUCED LESIONS OF THE KIDNEY¹

Glomerulonephritis

Penicillamine, Gold, Captopril, Sulphonamides, Rifampicin

Interstitial nephritis

Diuretics, Furosemide, NSAIDs, Rifampicin

Acute tubular necrosis

Aminoglycosides, Amphotericin, Cyclosporin.

Tubular obstruction

Methotrexate, Anticholinergics

PHARMACOKINETIC CHANGES IN RENAL FAILURE

1. ABSORPTION

Drug absorption in patients with renal failure may be altered secondary to gastrointestinal edema, gastric pH, vomiting, diarrhea, and delayed gastric emptying, gastrointestinal transit time.⁸ Specific drug interaction involving decreased absorption secondary to chelation manifest in patient taking phosphate binding acids containing aluminum or calcium.⁹ The elevated gastric pH may impair the dissolution process of other enterally administered medications, leading to incomplete drug absorption, particularly with acidic drugs.¹⁰ Metoclopramide or erythromycins are frequently administered to enhance the motility of the gastrointestinal tract. When these agents are administered, enteral absorption of medications is often decreased

due to an increase in gastrointestinal transit.

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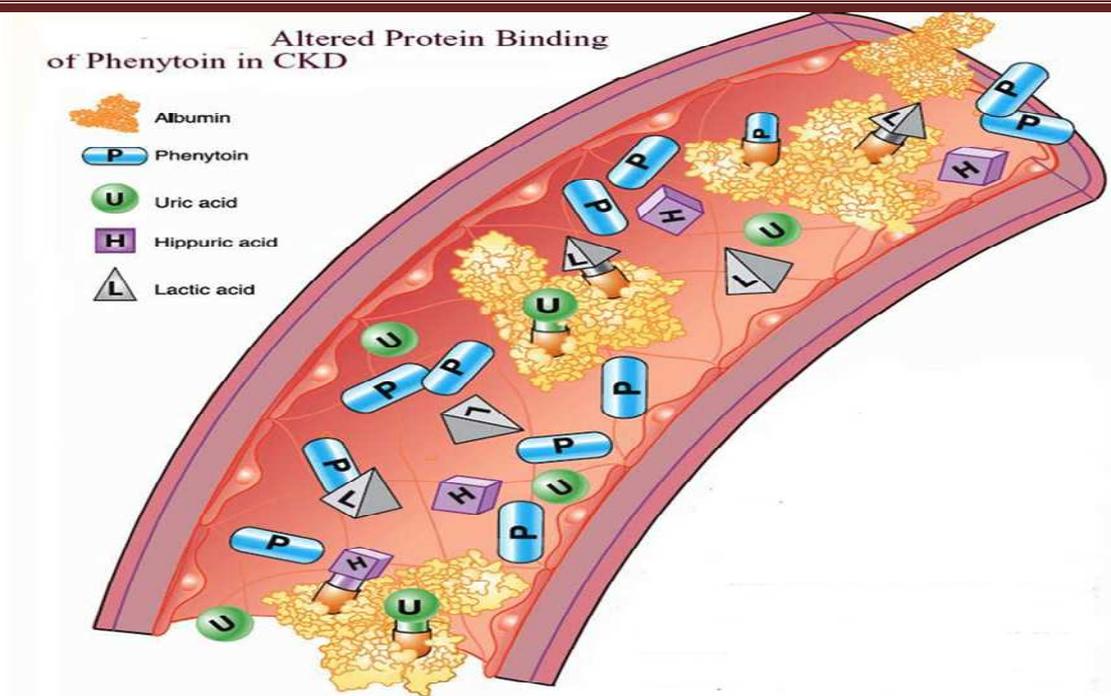
Bioavailability of Drugs in Patients with Renal disease ¹²

Decreased	Unchanged	Increased
D-Xylose	Cimetidine	Dihydrocodeine
Furosemide	Ciprofloxacin	Oxprenolol
Pindolol	Trimethoprim	Bufuralol
	Sulfamethoxazole	Propranolol

2. DISTRIBUTION

Altered plasma protein binding in critically ill patients with renal failure can significantly change drug distribution. Drugs that bind to plasma proteins exist in a state of equilibrium between unbound (free) and bound drug (not free). Unbound drug exerts a pharmacologic effect, decreased binding increases the amount of drug available to exert a pharmacologic effect and therefore increases the risk of toxicity. Anionic (acidic drugs) + albumin, Cationic (basic drugs) + alpha 1-glycoprotein.¹³ Drug-drug interactions do not occur primarily due to alteration in plasma protein binding, but they also occur in patients with poor renal

function due to changes in the configuration of albumin.¹⁴ Plasma protein binding can also be reduced in conditions such as the nephrotic syndrome, proteinuria, conditions that alter the molecular structure of albumin.¹³ Decreased binding of drugs to albumin in patients with renal failure is thought to be due to the accumulation of small acidic molecules displacing these drugs from binding sites or alterations in binding sites on the albumin molecules. This can lead to higher free fractions of drugs and potentially increase the risk of toxicity. Phenytoin is an excellent example of a drug with an increased Vd resulting from changes in protein binding related to CKD.¹⁵



3 METABOLISMS

Drugs oxidized by the cytochrome P-450 2D6 isozyme are more likely to be affected.¹⁶ Critically ill patients often have impaired metabolic function from nonrenal causes either from direct damage to the liver (cirrhosis), decreased blood flow to the liver (shock) or as a result of other medication that is an enzyme inhibitor or inducer.¹⁷ Some hepatically metabolized drugs have active metabolites that are excreted renally. In renal impairment these metabolites can accumulate and lead to drug toxicity.

For example¹⁸

Acetaminophen - N-acetyl-p-benzoquinoneimine (hepatotoxicity)

Procainamide - N-acetylprocainamide (cardiac toxicity)

4 ELIMINATION

As kidney function declines, the renal clearance of a drug decreases and the half life of renally excreted drug lengthens. Depending on the pKa value of drugs, the pH difference between plasma and tissue compartments may alter the ionization of drug molecules and therefore affect tissue redistribution versus clearance.¹⁹

Drugs with pH-Dependent Elimination

Weak Acids: Phenobarbital, Salicylates, Sulfonamides

Weak Bases: Amphetamines, Ephedrine, Procanamide, Quinidine, N-acetylprocainamide

NORMAL RENAL EXCRETION OF ANTIMICROBIAL DRUGS

The kidney is the primary organ responsible for the excretion of drugs and their

metabolites. The rate of elimination of drug by the kidney depends on the plasma concentration, the molecular size and the glomerular filtration rate (GFR), tubular handling and the degree of protein binding. The three main processes by which the kidney excretes drugs include Glomerular filtration, Tubular secretion, and Tubular reabsorption.²⁰

OFLOXACIN CONCENTRATIONS AFTER MULTIPLE ORAL DOSES²¹

GROUP	DRUG CONCENTRATION(µg/ml)		
	12 hr	24 hr	48 hr
Normal subject (GFR > 80 ml/min)	2.60	--	--
Mild impairment (GFR 30-80 ml/min)	4.02	2.68	2.05
Moderate impairment (GFR 20-30 ml/min)	4.13	2.59	1.80
Severe impairment (GFR < 20 ml/min)	5.87	3.70	2.45

DRUG EXCRETION IN RENAL FAILURE

1) Effects of Impaired Glomerular Filtration on Drug Elimination

Impairment of glomerular filtration can lead to a clinically significant accumulation of drug and /or its metabolites. To assess the likely impact of decreased glomerular

filtration, it is important to know what fraction of a drug is renally eliminated, as well as the excretion method for any active or toxic metabolites.^{11, 20} There are many factors influencing the amount of drug

filtered at the glomerulus. Table 1 lists these factors and how they influence drug filtration.

Table 1
Factors Influencing Glomerular Filtration of Drugs

FACTORS	EFFECT ON GLOMERULAR FILTRATION
Hydrostatic pressure	Drug filtration decreases as hydrostatic pressure decreases
Plasma protein binding	Drug filtration decreases as plasma protein binding increases
Volume of distribution	High volume of distribution decreases the amount of drug available to be filtered
Molecular size	Drug filtrations decreases as molecular size increases (MW less than 5 kDa and radii less than 15 Å)
Glomerular integrity	Drug filtration increases as membrane integrity decreases
Number of functioning nephrons	Drug filtration decreases as the number of functioning nephrons decreases

2) Effects of impaired tubular secretion on drug elimination

As mentioned before, 20% of the plasma flow is filtered at the level of the glomerulus. The remaining 425–600 ml/min of renal plasma flow not filtered at the glomerulus is directed to the peritubular capillaries, where drugs may be secreted. Tubular secretion is an active process where drugs are transported by membrane proteins from the interstitial fluid surrounding the proximal tubule and secreted into the lumen.

Tubular secretion rate depends on the intrinsic activity of the transporter, proximal tubule blood flow, and the percentage of free or unbound drug. There are two main transport systems for drugs in the proximal tubule. One transport system is for anions and the other transport system is for cations. Drugs can compete for secretion with other drugs and endogenous substances secreted by the same transporter, since they are saturable.¹¹ an example of competition for secretion via an anionic transporter is

probenecid with penicillins or cephalosporins. This combination has been used to prolong the half-life of penicillin.

3) Effects of impaired tubular reabsorption on drug elimination

Tubular reabsorption of drugs can occur by active and/or passive processes. When ultra filtrate passes through the nephron, up to 99% of the filtered volume is reabsorbed. This can lead to a dramatic increase in a drug's concentration in the tubule as the volume decreases. This high concentration

gradient of drug between the renal tubule and plasma promotes passive diffusion from inside the tubule into the plasma. The properties that effect passive tubular reabsorption are listed in Table 2. Altering urine pH has long been used to decrease the amount of drug reabsorbed and enhance excretion. Alkalinizing the urine can be used to enhance the elimination of barbiturates (weak acids) by increasing the fraction of ionized drug, which decreases the amount available for reabsorption.^[12] Table 3 lists some drugs with PH dependent elimination.

Table 2.

Factors Influencing tubular reabsorption of Drugs:

FACTORS	EFFECT ON TUBULAR REABSORPTION
Lipid solubility of the drug	Increased reabsorption with increased lipid solubility
Degree of ionization of the drug	Decreased reabsorption with increased ionization
Urine pH	Variable depending on if drug is acidic or basic
Urine flow	Decreased reabsorption as urine flow increases
Concentration gradient	Increased reabsorption as concentration gradient increased

Table 3.

Lists some drugs with PH dependent elimination

WEAK ACIDS	WEAK BASES
Phenobarbital	Amphotamines
Salicylates	N-acetylprocainamide
Sulfonamides	Procainamide

DOSAGE REGIMEN ADJUSTMENT

Dosage regimen adjustment is mainly considered in renal diseases, when the drug is mainly (at least 70% of the dose) excreted by the kidney either unchanged or as an active metabolite or the therapeutic window of the drug or the metabolite is narrow. Kidneys have been found to have many drug metabolizing systems, and it is likely that renal disease alters renal drug metabolism as well as hepatic metabolism.²²

Change in glomerular filtration rate (GFR) is considered the best overall indicator of both the renal dysfunction as well as the change in drug renal clearance. Dosage regimen adjustment options involve (i) reduction of the dose level, (ii) extension of the dosing interval, (iii) administration of a loading dose, and/or (iv) therapeutic drug monitoring.²³

CONCLUSION

In conclusion, variation in response to drugs occurs through many reasons that include majorly the state of disease influencing kidney functioning. Renal impairment alters renal excretion of drug or its metabolites. Considering the rational application of drug for the treatment in animals or human, dosages of drugs are required to adjust either by reducing dose or increasing dosage interval in renal impairment. Half life and clearance is altered and lead to over exposure of drugs to body, toxicity. PK varies from patient to patient and drug to drug in disease conditions. For dose adjustment in kidney diseases GFR and C_{cr} gives good indication about renal function.

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